and fluid in the pleura, are even more concealing and confusing. Often the primary growth, whether bronchial or parenchymal, is accompanied by metastatic nodular or miliary lesions in one or both lungs. Although the fact of metastasis is obvious, the examiner is likely to assume that the primary focus is extrathoracic, because pulmonary carcinoma usually originates in other parts of the body. Accumulations of fluid in the pleural sac are not at all rare. If the amount of transudate is small or only moderate, the primary signs are not appreciably altered, but often the cavity is completely filled, and the entire lung is obscured by a dense shadow. In the latter condition, unless the patient is reëxamined after paracentesis, the nature of the pulmonary disease cannot be determined.

In short, although the roentgenologist will often be the first to discover signs of pulmonary carcinoma or vaguely suspect its presence, he can seldom make a positive diagnosis without clinical aid. On the other hand, the clinician will usually require the stimulus of the roentgenologic report to orient his investigations, and he will certainly need the help of the roentgenologist and the bronchoscopist in making the final diagnosis. When the roentgenogram reveals the shadow of a mass, either in the hilum or in a lobe, which cannot confidently be attributed to one of the more common intrathoracic diseases, primary carcinoma of the lung is to be thought of, especially if the patient is of cancer age, if weight loss is extreme, and if the history is atypical. If the mass is in the hilum, bronchoscopy is indicated.[5]

In cases in which either atelectasis or bronchiectasis is the most striking feature in a roentgenogram of the chest, the corresponding hilum should be scanned for evidence of bronchial carcinoma (Fig. 6).

In cases in which fluid conceals all or most of the pulmonary field and an affirmative diagnosis of the underlying lesion cannot be made with confidence, roentgenologic examination should be repeated after paracentesis, for the lesion may be a carcinoma.

METASTASIS

Malignant disease of the lung often produces metastasis in the brain. I have seen two patients who came to the clinic primarily for treatment of an intracranial lesion. In both instances a casual roentgenologic examination of the chest, made as a routine, revealed the typical manifestations of primary malignant lesion. As a result of this experience I feel justified in urging examination of the chest as a routine in cases presenting symptoms localized in the brain, as they may be due to metastasis to the brain from carcinoma of the lung.

If pulmonary metastasis, either nodular or miliary, is obvious roentgenologically, and this report is fully warranted, it must not be assumed too hastily that the primary growth is extrathoracic, although it usually is. The examiner should consider the possibility of a primary focus in the lung, the roentgenogram should be inspected for a shadow of unusual form and size, and the clinician should consider primary carcinoma of the lung among alternatives.

Thus far, with few exceptions, carcinoma of the lung, especially the bronchial variety, has been a hopeless condition. Harrington,[2] however, is of the opinion that if the lesion can be recognized early, lobectomy may be performed, thus affording a more optimistic prognosis. Certainly these patients have everything to gain and nothing to lose by such a procedure. Therefore, every effort possible should be made to recognize the carcinoma early. The most essential factor in the diagnosis is keeping the disease in mind.

The Mayo Clinic.

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THE PHYSIOLOGIC AND PATHOLOGIC SIGNIFICANCE OF THE LIPOCHROMES*

By CHARLES L. CONNOR, M. D.
San Francisco

LIPOCHROMES are yellow to red pigments which occur mostly in plants, the most important of which are carotin, xanthophyll, and lycopin. The first of these is most abundant in carrots and green vegetables; the second, in yellow leaves; and the third is the red pigment of tomatoes. The name "lipochrome" has been given to them because of their almost constant association with lipoids in the animal body, and because they have in general the same characters as regards solubility and extraction. They are, however, in no sense lipoids. They are unsaturated hydrocarbons or oxyhydrocarbons, cannot be produced from lipoids, and do not combine with fatty acids. They are relatively inert chemically; are soluble in fats, unite with the halogens and oxygen, and can be extracted from tissues by petroleum, ether, chloroform, and other fat solvents. Upon oxidation they become colorless.

Their function, even in plants where they are most abundant, has not been determined. They are almost always associated with chlorophyll, but remain in leaves after the chlorophyll has disappeared. They are sometimes the only pigments in etiolated leaves, and here seem to take the place of chlorophyll. They probably, in plants, have a respiratory function, or have to do with photosynthesis in some way.[1]

* From the Department of Pathology, University of California Medical School.
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RÉSUMÉ OF EXPERIMENTAL WORK ON LIPOCHROMES

It has been rather definitely shown by Palmer,[2] van den Bergh and Snapper,[3] and others that lipochromes appear in the animal body only after the ingestion of food containing carotin or xanthophyll. It cannot be demonstrated that they have any function in animals, or that, indeed, they are of any particular importance. Chickens deprived of xanthophyll continue to grow in the same manner as when fed well-colored food (Palmer and Kempster).[4] Drummond[5] reported the failure of pure crystalline carotin, fed at the rate of 0.003 per cent of the ration, to replace vitamin A in the diet of rats. Steenbock, Boutwell, and Kent[6] noted the close association of carotin and vitamin A in plants, but stated that vitamin A was not carotin. Later Steenbock[7] advanced the provisional assumption that this vitamin is one of the carotinoid pigments, and in still later papers by Steenbock and his associates,[8] they show that yellow pigments are almost inseparable from vitamin A of plants. Palmer[9] discusses this work critically, and believes the evidence in favor of the identity of carotin and vitamin A is not sufficient. In fact Steenbock, Sell, and Buell[10] could not obtain the same correlation between vitamin content and pigmentation when comparing animal products such as cod-liver oil, butter fat, perinephric fat, and egg yolk. Drummond and Coward[11] noted this lack of association of pigment content and vitamin A content in a large number of fats and oils. Colorless dog fat and colorless perinephric fat were rather rich in vitamin A. Palmer and Kennedy[12] found that albino rats grew and reproduced normally on diets in which 5 to 9 per cent of ewe milk fat (containing 0.00014 per cent carotin) furnished the vitamin A, and that growth was normal when carotinoid-free egg yolk from hens upon a carotinoid-free diet furnished the vitamin A. Coward and Drummond[13] found that the synthesis of vitamin A in plants increases as the chlorophyll content increases. They also demonstrated little, if any, fat-soluble vitamin in yellow seedlings and red seaweeds, both of which contained abundant carotinoid pigment, but no chlorophyll.

Wiehuizen[14] and others noted the low lipochrome content of the blood serum in human beriberi, and stated that vegetables with a high lipochrome content also have a high antiberiberi value. McCarrison[15] also noted that highly colored butter fat gave greater protection against edema of the adrenals of pigeons fed on autoclaved rice than poorly colored butter. The suggestion is then made that one of the fractions of vitamin B may be a lipochrome. This is further suggested by Underhill and Mendel,[16] who cured a pellagra-like disease in dogs (a deficiency disease reported by Crittenden and Underhill[17] in 1917) by adding colored egg yolk, highly colored butter, carrots or, finally, pure crystalline carotin to the diet. Goldberger,[18] however, stated that carrots contain relatively little substance that will prevent black tongue in dogs, and will not prevent human pellagra.

REPORT OF AUTHOR'S EXPERIMENTAL WORK

My own experiments have been inconclusive. Twelve guinea-pigs upon a carotin-free diet lost weight rapidly and all died (except two which were killed) in a period of a month. The diet consisted of white turnips, white cabbage, white cornmeal, and oatmeal cakes prepared with Mendel's salt mixture (sodium chlorid, calcium lactate, magnesium citrate, ferric citrate), with filter paper. Pure carotin in olive oil did not supply the lacking food element. These experiments were not designed, however, to test out the vitamin content of carotin, and were poorly controlled. I determined the amount of carotin intake in a guinea-pig used by Wolbach and Howe[19] as a control animal. This had been on a synthetic diet for two years, receiving all its carotin and xanthophyll in five cubic centimeters of orange juice daily. The daily intake of carotin was 0.002 milligrams; of xanthophyll, 0.07 milligrams. The animal was in perfect health.

From these results it may be concluded that vitamin A and carotin have almost the same solubility properties, and are very closely associated in plants, but that one may be present in some substances without the other. Carotin takes the place of the deficient substance in a diet which causes Crittenden and Underhill's disease in dogs, and this disease appears to be associated with black tongue in dogs and pellagra in man. In view of the contradictory results of Underhill and Goldberger, however, no conclusion can be arrived at concerning the relationship of carotin to vitamin PP,* nor, in fact, to any vitamin.

The effect of feeding lipochrome to animals differs with the animal in question. Practically all, of course, ingest it regularly with food. But the rabbit, guinea-pig, and many other animals do not store it in their adipose tissue. It is present in the fat of man, horse, cow, chicken, and others. Even when fed in concentrated form to rabbits and guinea-pigs, or injected intravenously or intraperitoneally into these animals, the fat does not become colored.[20] It is present in the blood of those animals which have colored fat, and is not found in detectable amounts in the blood of animals with colorless fat (van den Bergh, Palmer, Connor).

The cycle of xanthophyll in chickens has been observed by Palmer and his associates. It is taken in in yellow corn and green plants, appears in the fat and skin, and later in egg yolk. The density of color of egg yolk depends directly on the diet and indirectly on the number of eggs laid. When a diet low in lipochrome is fed, or when a large number of eggs are being laid, the skin and fat become pale, and the egg yolks colorless. In the chicken, then, one way of excretion is through the ovary, and in this and other animals it is excreted by the skin (Palmer), the sebaceous glands, and, in man, according to Hess and Myers,[21] the urine. I could not confirm this last in guinea-pigs and rabbits, nor in one adult to whom pure carotin in olive oil was fed.

Lipochrome was present in the adrenal glands

* Pellagra preventive.

in all animals studied by van den Bergh, Muller and Brockmeyer,[22] and by Connor.[23] It has been found in the blood, fat, skin, liver, spleen, adrenals, and corpus luteum of man, in the liver and adrenals only of rabbits and guinea-pigs; and in the skin, fat, and egg yolk of chickens. It was not present in any organ of a three months' old infant.

The maximal effect of carotin feeding is produced in diabetics upon a diet of green vegetables. The condition called "xanthosis diabetica" has been known since 1913 to be associated with an increase of lipochrome in the blood. Numerous cases of carotinemia have been reported in Germany in diabetics,[24] in children under asylum conditions, or in adults upon semi-starvation diets during the war. A few have been reported in this country since 1919 in children (by Hess and Myers)[21] and in diabetics (by Head and Johnson,[25] and by Stoner).[26] A yellow coloration of the skin had been noticed by Baelz [27] in 1896, in Japanese upon diets of yellow vegetables. He called the condition "aurantiasis cutis." In nearly all these cases the condition has cleared up upon reduction of the amount of green vegetables ingested. But it is to be noted that certain diabetics frequently show a yellowish coloration of the skin even when, by the use of insulin, they are taking essentially normal diets, and such a patient is usually in the class of the severe diabetic, and has a high blood cholesterol. Also, carotinemia has never been reported in individuals who have been upon otherwise normal diets. Rabinowitch [28] believes that persistent carotinemia has about the same significance in diabetes as a persistently high blood cholesterol, that is, a doubtful prognosis. It was noted by Rabinowitch, and by myself, separately, that the average amount of carotin in normal blood is about 0.06 mg. per cent, and that in diabetic blood it is usually over 0.1 mg. per cent.

METABOLIC CYCLE IN MAN

In man the metabolic cycle seems to be as follows: Lipochrome is ingested with the food, is absorbed only partly, probably along with cholesterol by way of the portal system as well as by lymphatics, appears in the blood stream in higher concentration during the period of fat absorption, then falls in amount as the amount of fat decreases, *i. e.*, in about four hours. Some of it is carried to and deposited with lipoids in structures where fat is being stored or used in the formation of new tissues. These latter consist normally of the adrenal cortex, where lipoids appear necessary for cell metabolism, the corpus luteum, the sebaceous glands, and the skin. Pathologic lesions in which lipochromes appear are those structures to which lipoids contribute or form an essential factor, namely, xanthomas, atheromatous patches in the aorta, pathologic accumulation of fat in the spleen, liver, heart, or other organs, and lipomas.

That lipochromes may be broken down by the liver is indicated by the following experiment: Four rabbits were fed pure carotin in olive oil. Four hours later blood from the right heart and from the peripheral circulation contained no carotin, but blood from the portal vein contained from a trace to 0.01 mg. per cent. The liver from these animals always contained carotin, but none was found in the bile. It is possible that what little carotin is absorbed from the intestine of these animals is broken down by the liver. Simple oxidation would render it colorless, and so its further progress could not be followed. Most of it, changed and unchanged, is excreted by the intestinal tract. The feces of all animals examined (man, rabbit, guinea-pig, rat) contained abundant lipochrome. There is only one positive experiment to the effect that carotin is excreted in the urine (that by Hess and Myers). All others have been negative or inconclusive.

SUMMARY

1. Lipochromes seem to be inert substances which are taken into the body in the food, and because of their solubility in fat, are stored where fat accumulates. They are not present at birth in infants, nor in other animals.

2. Carotin is closely associated with vitamin A in plants, but the two are separable. It exerts some influence upon conditions associated with vitamin B deficiency, but definite evidence that it will cure beriberi or pellagra is lacking.

3. In those animals which absorb lipochrome it is stored where lipoids appear normally or abnormally. The most notable places under normal conditions are: adipose tissue, adrenals, corpora lutea, and sebaceous glands; of abnormal conditions, xanthomas, lipomas, atheromas, and fatty infiltrations of liver, spleen and heart, are the most important.

4. Certain animals do not store up lipochrome, probably for two reasons: first, because very little is absorbed from the gastro-intestinal tract, and, second, because what little is absorbed passes into the portal system, and is broken down by the liver.

5. Normal human blood commonly but not constantly contains carotin in measurable amount. It is slightly increased in the blood of diabetics, and in these it may be associated with lipemia. Normally it is increased in the blood within two hours after the ingestion of carotin. It is excreted by the intestinal tract, and the skin and sebaceous glands. It does not appear in the urine.

6. There is no evidence that lipochrome is synthesized in the animal body or that it enters into any metabolic process.

University of California Medical School.

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MONOCULAR OCCLUSION IN APPARENTLY ORTHOPHORIC EMMETROPES*

By RODERIC O'CONNOR, M. D.

Oakland

MY first paper on this subject appeared in the *British Journal of Ophthalmology* of 1924. It gave the results in a series of cases, and was intended to confirm and reinforce Marlow's work.

My second paper was before the 1926 meeting of the American Academy of Ophthalmology and Otolaryngology. In that paper were listed 110 patients who were apparently orthophoric but whose symptoms persisted after accurate correction of refractive errors.

In this paper I wish to list a series of emmetropes who were apparently orthophoric. All had persistent discomfort, related to the use of the eyes, severe enough to persuade them to carry out the prolonged monocular occlusion test in hopes of finding the cause of their symptoms.

In looking over my records I found at least as many similar cases who failed to carry out the test and many times the number listed who were practically emmetropic and whose muscle balance was within the degree of variation from orthophoria that is usually considered of no importance.

I am including only those who came under the strict limitations of the title in order to shorten the table and to make more emphatic the importance of the test.

In this connection I wish to state that I prove my operative results by occlusion, figuring that my work is not finished till the patient tests within the allowable variation from normal behind the patch.

This shows two things:

1. There is no need to fear the production of an opposite condition, provided, of course, that the right operation has been done at the right place.

2. The test behind the patch is the true one, exactly as the refraction under cycloplegia is the true test in that respect. In each instance the muscles involved have been put at rest.

In order to forestall the usual suggestion of a discusser I want to admit here that, if a series of *apparently normal and comfortable* eyes were patched, many would show muscle deviations, exactly as the cycloplegic discloses the true refractive error. The answer is that we are only interested in those patients who are in trouble. Because one patient may have no symptoms from a three-degree hyperphoria is no sign that another may not. In any event the occlusion test proves matters one way or the other.

The other point usually brought up in discussion is the question of accurate refraction. Ignoring the implication, I wish to state that many patients are perfectly comfortable with the hook-front prisms worn over an old correction that is known to be far from correct, and many others are comfortable with a prism correction alone when there are worthwhile amounts of ametropia present. All of which proves that moderate degrees of refractive error frequently fail to produce symptoms, just as errors of muscle balance so fail. Sometimes I see patients wearing spheres of a quarter diopter prescribed by oculists. I consider such a prescription to be an admission of ignorance of the cause of the symptoms.

Several years ago Doctor Burleson of San Antonio wrote an article praising highly an operation, devised by another Texan, for the relief of trachomatous lid troubles. He stated that, in all probability, American ophthalmologists would ignore the operation because it had not been invented by someone in central Europe with an unpronounceable name. I feel much the same in regard to the occlusion test. Had its discoverer been able to sign his name Ivan Awfulitch instead of Marlow the chances are that American ophthalmologists would have taken it up at once.

In my opinion only the unscientific and gullible type of mind can resist the proof, contained in the appended table, of Marlow's contention that

* Chairman's address, Eye, Ear, Nose and Throat Section, California Medical Association, at the Fifty-Eighth Annual Session, May 6-9, 1929.